REMARKS

Reconsideration of this application is respectfully requested.

A complete listing of the claims (85-113) is provided above. Of these, claims 85-110 are pending and were previously presented. Four claims (85, 104 and 108-109) have been amended. New claims 111-113 have been added.

Claims Amendments

In a sincere effort to define their invention with more clarity, Applicants have amended claims 85, 104 and 108-109. In claim 85 which is directed to a first vector, a defining feature has been added in the form of the phrase "wherein said second viral vector lacks retroviral sequence (i)." Support for this feature is found variously in the specification. See, for example, Figures 8, 9, 10, 11, 12 and 13. In claim 104, the fourth element (iv) has been amended to recite "packaging component or components for producing a non-retroviral vector." Support for this feature is found variously in the specification. See, for example, page 27, first full paragraph, continuing through page 28, second full paragraph. Finally, claims 108 and 109 have each been amended to correct an antecedent problem (rejection under 35 U.S.C. §112, second paragraph, October 7, 2005 Office Action, page 7). Thus, the previously recited "second viral vector" has been changed to "non-retroviral viral vector sequences."

It is believed that none of the foregoing amendments constitutes the insertion of new matter into Applicants' original disclosure.

Entry of the above claim amendments is respectfully requested.

New Claims

In the October 7, 2003 Office Action (page 7), it was indicated that "[c]laims 96, 98 and 100 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." In presenting new claims 111-113, Applicants have adopted the Examiner's suggestion which is greatly appreciated. New claims 111-113 are each directed to a packaging cell line. Claim 111 recites a packaging cell line lacking a receptor for the first vector, thus incorporating the limitations of claim 96 into base claim 85. Claim 112 recites a packaging cell line lacking a receptor for the second vector, thus incorporating the limitations of claim 98 into base claim 85. Finally, claim 113 recites a packaging cell line lacking a receptor for both the first vector and the second vector, thereby incorporating the limitations of claim 100 into base claim 85.

None of the new claims 111-113 is believed to constitute the insertion of new matter into the original specification.

Entry of new claims 111-113 is respectfully requested.

Before addressing the art-based rejections, Applicants would respectfully point out that in each of the four cited documents (Miller et al., Wong-Staal et al., Curiel and Finer et al.), the disclosed second vector is a retroviral vector. In contrast to these cited documents, the first vector of the present invention is a retroviral vector which produces a non-retroviral vector (second viral vector).

The First Rejection Under 35 U.S.C. §102

Claims 85-86, 92-94, 97, 101 and 103 stand rejected under 35 U.S.C. §102(b) as being anticipated by Miller et al. ["Improved Retroviral Vectors for Gene

Transfer and Expression," BioTechniques 7:980-990 (1989)]. In the October 7, 2003 Office Action (pages 2-3), it is stated:

> Applicants claim a first viral vector comprising retroviral sequences (i.e. LTR sequences), a retroviral packaging component(s), non-retroviral viral vector sequences, and a nucleic acid sequence coding for a exogenous gene or exogenous nucleic acid sequence wherein when introduced into a packaging cell (which provides one or more packaging components for the second vector), said first vector produces a second viral vector comprising said non-retroviral vector sequences, a promoter or terminator and the exogenous nucleic acid sequence(s). Applicants also claim a packaging cell (which can be derived from NIH 3T3 cells) comprising a receptor for the second vector and wherein the packaging components for the second vector are expressed transiently from non-integrated sequences.
>
> It is noted that a retroviral packaging component can be a retroviral packaging signal sequence.
>
> Miller et al. (BioTechniques, 1989, Vol. 7, No. 9, pp. 980-990, see whole article, particularly Figures 1-3, right column on p. 981, first two columns on p. 986) recites a first DNA vector (i.e. LNCX, LNSX, etc.) comprising retroviral sequences (i.e. LTRs), a retroviral packaging component (packaging signal sequence), non-retroviral viral vector sequences (i.e. SV40 or CMV promoters) and a sequence encoding a exogenous gene (neo) wherein the first vector upon introduction into a packaging cell line produces a second vector (retroviral vector RNA sequence (comprising a promoter) to be packaged into infectious retroviral particles). Miller et al. also recites a packaging cell line (which can be NIH 313 cells) and packaging cell lines (PA317) comprising a receptor for the retroviral vector particles produced by said cell wherein the packaging components are expressed transiently from non-integrated sequences. Miller et al. therefore teaches the claimed invention.

The anticipation rejection is respectfully traversed.

As indicated above, the present invention is directed to viral vector technology in which the first vector is a retroviral vector which produces a non-retroviral vector (second viral vector), as set forth in claim 85 as amended. In the case of Miller et al., a first retroviral vector is used to make a second viral vector.

In claim 104, packaging component or components for producing a non-retroviral vector is now recited, and this feature is again lacking in Miller's paper.

In view of this lack of identity of material elements between Miller et al. and the presently claimed invention, Applicants respectfully request reconsideration and withdrawal of the first rejection under §102.

The Second Rejection Under 35 U.S.C. §102

Claims 85-94 and 103-107 stand rejected under 35 U.S.C. §102(e) as being anticipated by Wong-Staal et al., U.S. Patent No. 5,650,309 (issued July 22, 1997). In the Office Action (pages 3-4), it is stated:

> Applicants claim a first vector comprising retroviral sequences, retroviral packaging component(s), non-retroviral viral vector sequences and nucleic acid sequences coding an exogenous gene or exogenous nucleic acid sequence wherein when introduced into a packaging cell (providing one or more packaging components for the second vector), said vector produces a second viral vector comprising said non-retroviral viral vector sequences and said exogenous gene or nucleic acid sequence. Applicants also claim packaging cell lines wherein the packaging components for the second vector are derived from transient expression of non -integrated nucleic acid sequences.
>
> Wong-Staal et al. (previously cited by the examiner, see whole document, particularly Figs. 11-13, Claims 1-14, columns 6-7, 12 and 16-18) recites a first vector (which can be a DNA plasmid vector) comprising retroviral sequences (such as LTRs), retroviral packaging components (i.e. gag or pol or env or a combination of two or more components, etc.), non-retroviral viral vector sequences (AAV sequences such as AAV ITR elements) and nucleic acids encoding a anti-viral protein or antisense nucleic acid wherein said vector produces a second vector (retroviral RNA vector) upon introduction of the first vector into a packaging cell which provides one or more packaging components (derived from transient expression of non-integrated nucleic acid sequences) for the second vector. Wong-Staal et al. also recite a cell line comprising retroviral sequences (such as LTR sequences), non-retroviral viral vector sequences such as the AAV ITRs, nucleic acid sequences coding for an exogenous gene or nucleic

acid sequence and packaging components (provided in helper plasmids) for the AAV vector sequence. Wong-Staal et al. therefore teaches the claimed invention.

The anticipation rejection is respectfully traversed.

As indicated above, the present invention is directed to viral vector technology in which the first vector is a retroviral vector which produces a non-retroviral vector (second viral vector), as set forth in claim 85 as amended. In claim 104, packaging component or components for producing a non-retroviral vector is now recited. In the case of Wong-Staal et al., their first vector is a non-retroviral vector, namely, AAV, that generates a second vector which is a retroviral vector. Again, materiality in the form of the instantly claimed first vector (retroviral vector) which produces a second vector (non-retroviral vector) is lacking in Wong-Staal's disclosure.

Reconsideration and withdrawal of the second rejection under §102 is respectfully requested.

The Third Rejection Under 35 U.S.C. §102

Claims 85-86, 92-94, 95, 97, 99,101 and 103-105 and are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel, U.S. Patent No. 6,333,030 B1 (issued December 25, 2001). In the Office Action (page 5), it is stated:

> Applicants claim a first vector comprising retroviral sequences (i.e. LTR sequences), retroviral packaging component(s), non-retroviral viral vector sequences, nucleic acid sequences coding for an exogenous gene or exogenous nucleic acid sequence, wherein when introduced into a packaging cell said first vector produces a second vector comprising said non-retroviral viral vector sequences and said exogenous nucleic acid sequences as well as one or more promoters, terminators, etc. Applicants also claim packaging cells (i.e. derived from NIH 3T3) comprising a receptor for the first vector and/or a receptor for the second vector and wherein the components for packaging are from transient expression of non-integrated nucleic acid

sequences.

Curiel (U.S. Patent 6,333,030, issued 12/25/01, priority to 02/04/97, see claims 1-10, the paragraph bridging columns 4-5, Examples 3-4, 18 and 21) recites a first vector (adenoviral vector) comprising retroviral sequences (LTRs), retroviral packaging components (packaging signal sequence), non-retroviral viral vector sequences (adenoviral vector sequences), nucleic acid sequences coding for an exogenous gene or sequence wherein when vector is introduced into a packaging cell (transiently expressing non-integrated sequences encoding packaging components for the second vector) protuces a second vector (retroviral vector) comprising the non-retroviral sequences and the exogenous gene or sequences. Curiel also recites packaging cells comprising retroviral sequences, non-retroviral viral vector sequences (adenoviral sequences), sequences encoding an exogenous gene and packaging components for' said non-retroviral vector (adenoviral) sequences. Curiel therefore teaches the claimed invention.

The third anticipation rejection is respectfully traversed.

As indicated above, the present invention is directed to viral vector technology in which the first vector is a retroviral vector which produces a non-retroviral vector (second viral vector), as recited in amended claim 85. Packaging component or components for producing a non-retroviral vector are now recited in claim 104. In the case of Curiel, his disclosed first vector is a non-retroviral vector, namely, adenovirus, that generates a second vector which is a retroviral vector. Thus, a material element in the form of Applicants' second viral vector which is a *non-retroviral* vector, is altogether lacking in Curiel's patent.

Reconsideration and withdrawal of the third anticipation rejection is respectfully requested.

<u>The Fourth Rejection Under 35 U.S.C. §102</u>

Claims 85, 86, 92-94, 97 and 101-1 02 are rejected under 35 U.S.C. 102(e) as being anticipated by Finer et al. In the Office Action (pages 6-7), it is stated:

Applicants claim a first vector comprising retroviral sequences (i.e. LTR sequences), retroviral packaging component(s), non-retroviral viral vector sequences and nucleic acids coding for an exogenous gene or exogenous nucleic acid sequence, wherein when introduced into a packaging cell line said first vector produces a second viral vector comprising said non-retroviral vector sequences, said exogenous gene or nucleic acid sequence (encoding a protein or antisense), one or more promoters or terminators, etc. and wherein said cell provides one or more packaging components for said second viral vector. Applicants also claim packaging cells (which can be 293 cells or NIH 313 cells) comprising a receptor for the second vector and wherein the sequences encoding the packaging components for the second vector are stably integrated into the genome of the packaging cell.

Finer et al. (U.S. Patent 6,218,187, issued 04/17/01, priority to 08/21/95, see whole document, particularly column 3, lines 30-67; column 4, lines 40-49; column 5, lines 31-56; paragraph bridging columns 5 and 6; paragraph bridging columns 11-12; Example 1, etc.) recites a first vector (a DNA plasmid vector) comprising retroviral sequences (LTR sequences), retroviral packaging components (retroviral packaging signal sequence), non-retroviral viral vector sequences (SV40 or CMV sequences), and nucleic acid sequences encoding a gene or nucleic acid sequence of interest wherein when said first vector is introduced into a packaging cell (293 cell) having the sequences encoding the packaging components integrated into the cell genome, a second vector (retroviral RNA vector) is packaged and generated. The 293 cells have a receptor for the second vector as they can be infected by said vectors. Finer et al. therefore teach the claimed invention.

The fourth anticipation rejection is respectfully traversed.

As indicated above, the present invention provides a first vector which is a retroviral vector that produces a non-retroviral vector (second viral vector), and this is recited in claim 85 as amended. Packaging component or components for producing a non-retroviral vector are now recited in claim 104. In the case of Finer et al., the only non-retroviral viral sequences are SV40 and CMV promoters. There is no disclosure or suggestion in Finer et al. for producing a non-retroviral vector.

In view of such a material element lacking in Finer et al., Applicants respectfully request reconsideration and withdrawal of the fourth rejection under §102.

The Rejection Under 35 U.S.C. §112

Claims 108-110 are rejected for indefiniteness under 35 U.S.C. 112, second paragraph. In the Office Action (page 7), it is stated:

> Claims 108-109 (and dependent claims) are vague in that there is no antecedent basis for the term "said second viral vector in the claim from which these claims depend.
>
> Claims 96, 98 and 100 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

As indicated above, claims 108-109 have been amended to delete "second viral vector" in favor of "non-retroviral viral vector sequences." In so doing, antecedent support has now been provided in both claims.

As also indicated above, new claims 111-113 have been added which adopt the suggestion and overcome the objection of claims 96, 98 and 100.

In view of the amendments to claims 108-109 and the addition of new claims 111-113, Applicants respectfully request reconsideration and withdrawal of the rejection under §112, second paragraph.

Submission of New Drawings

A Notice of Draftsperson's Patent Drawing Review was attached to the October 7, 2003 Office Action. In response to the Notice, Applicants are submitting herewith as Exhibit A new drawings in the form of Figures 1-13 (total of 10 sheets). It is respectfully requested that the new drawings (Exhibit A) be

processed and entered into this application in lieu of the original drawings submitted on March 24, 1998.

Notice of Appeal

Concurrently with this paper, Applicants are filing a Notice of Appeal with authorization for the small entity fee therefor.

Favorable action on this application is respectfully requested.

* * * * * * *

SUMMARY AND CONCLUSIONS

Claims 85-113 are presented for further examination. In the claim listing provided above, claims 85, 104 and 108-109 have been amended while claims 111-113 have been added.

The small entity fee for presenting new claims 111-113 is $200 based upon the presentation of two additional new independent claims above the previously paid three claims. The Patent and Trademark Office is authorized to charge the requisite $200 claim fee to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with this paper. In the event that any other fee or fees are due, however, the Patent and Trademark Office is authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

In view of the above discussion of the issues and amendments to the claims, Applicant respectfully submits that all of the instant claims are in allowable condition. Should it be deemed helpful or necessary, the Examiner is respectfully invited to telephone the undersigned at (212) 583-0100 to discuss the subject application.

Respectfully submitted,

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Registration No. 32,567
Attorney for Applicants

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EXHIBIT A

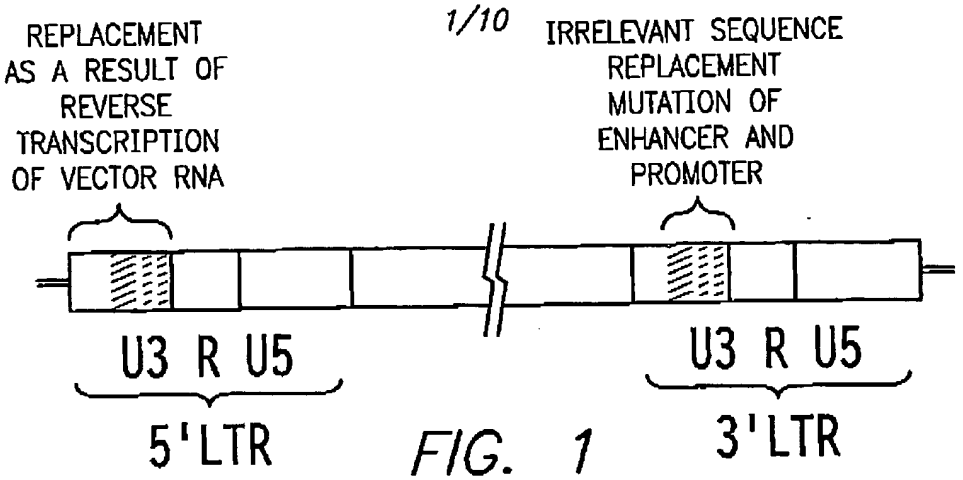


FIG. 1

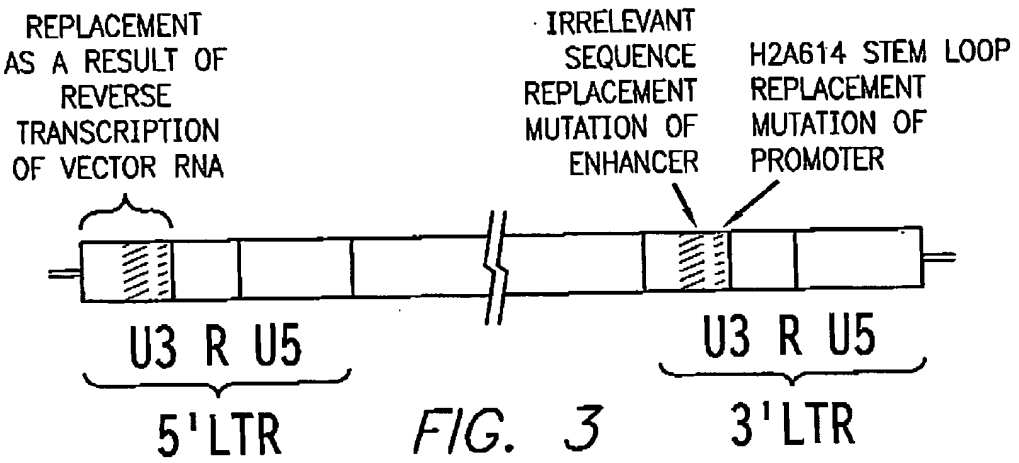


FIG. 3

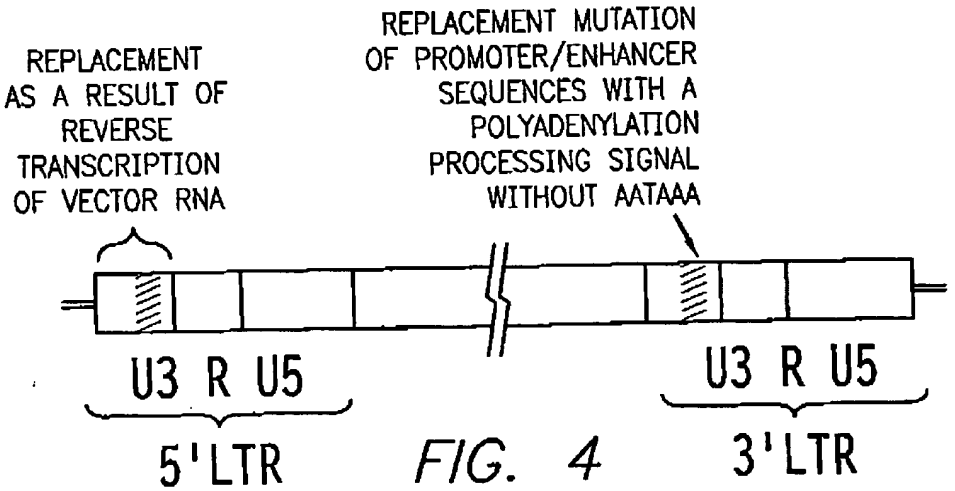


FIG. 4

Wild type 3' LTR sequence:

1	GAACAGATGG	AACAGCTGAA	TATGGGCCAA	ACAGGATATC	TGTGGTAAGC
51	AGTTCCTGCC	CCGGCTCAGG	GCCAAGAACA	GATGGAACAG	CTGAATATGG
101	GCCAAACAGG	ATATCTGTGG	TAAGCAGTTC	CTGCCCCGGC	TCAGGGCCAA
151	GAACAGATGG	TCCCCAGATG	CGGTCCAGCC	CTCAGCAGTT	TCTAGAGAAC
201	CATCAGATGT	TTCCAGGGTG	CCCCAAGGAC	CTGAAATGAC	CCTGTGCCTT
251	ATTTGAACTA	ACCAATCAGT	TCGCTTCTCG	CTTCTGTTCG	CGCGCTTCTG
301	CTCCCCGAGC	TCAATAAAA			

Corresponding modified 3' LTR sequence from pENZ1 (modified sequences in bold italics):

1	***ACGCTTGATC***	***CGGCTACCTG***	***CCCATTCGAC***	***CACCAAGCGA***	***AACATCGCAT***
51	***CGAGCGAGCA***	***CGTACTCGGA***	***TGGAAGCCGG***	***TCTTGTCGAT***	***CAGGATGATC***
101	***TGGACGAAGA***	***GCATCAGGGG***	***CTCGCGCCAG***	***CCGAACTGTT***	***CGCCAGGCTC***
151	***AAGGCGCGCA***	***TGCCCGACGG***	***CGAGGATCTC***	***GTCGTGAC***TT	TCTAGAGAAC
201	CATCAGATGT	TTCCAGGGTG	CCCCAAGGAC	CTGAAATGAC	CCTGTGCCTT
251	ATTTGAACTA	ACC***GG***TCAGT	TCGCTTCTCG	CTTCTGTTCG	CGCGCTTCTG
301	CTCCCCGAGC	TCA***GCTGCG***			

FIG. 2

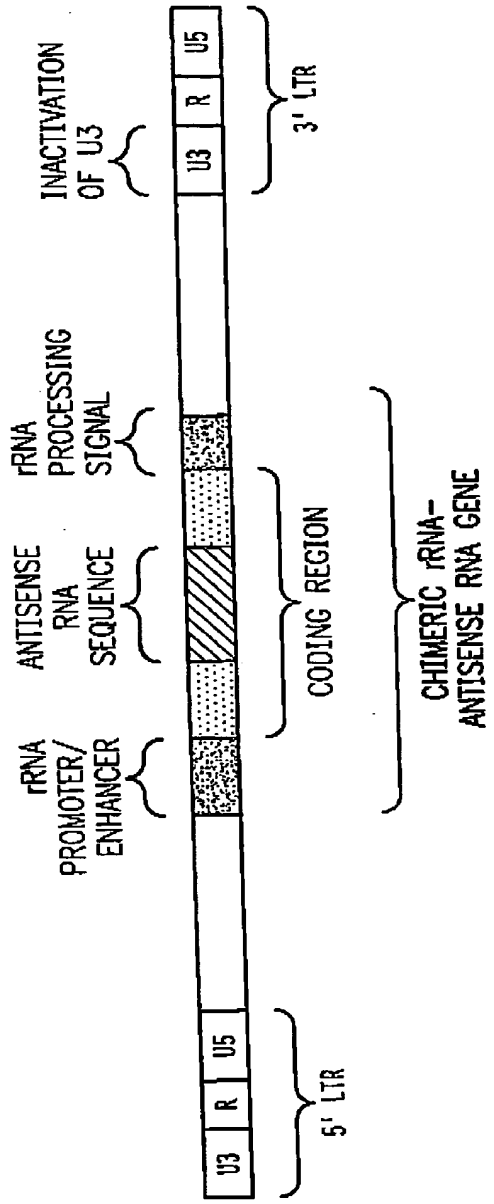

U3
R
U5
5' LTR
rRNA PROMOTER/ ENHANCER
ANTISENSE RNA SEQUENCE
rRNA PROCESSING SIGNAL
INACTIVATION OF U3
U3
R
U5
3' LTR
CODING REGION
CHIMERIC rRNA-ANTISENSE RNA GENE

FIG. 5

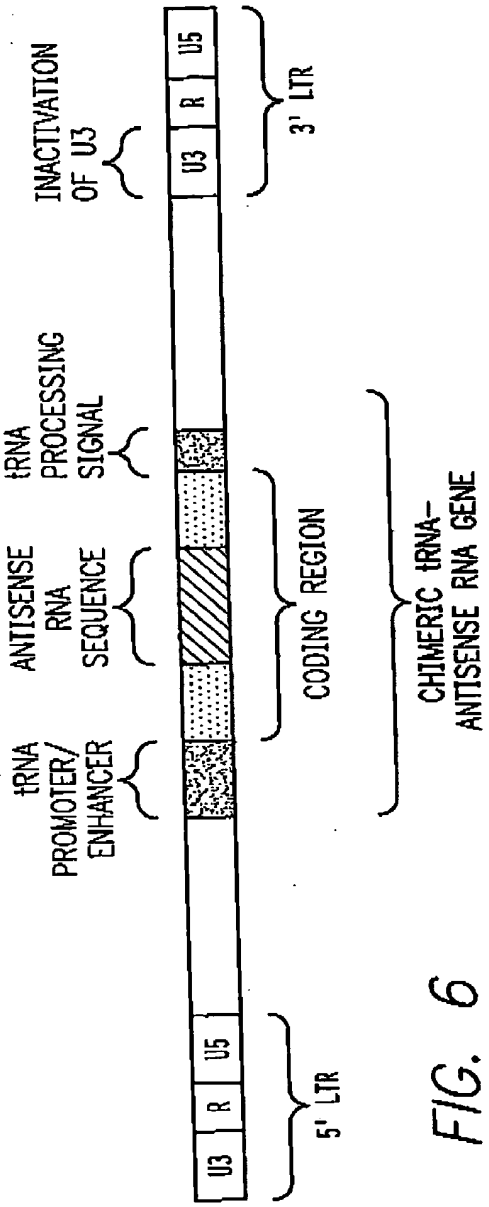

tRNA PROMOTER/ ENHANCER
ANTISENSE RNA SEQUENCE
tRNA PROCESSING SIGNAL
INACTIVATION OF U3
U3
R
U5
5' LTR
3' LTR
CODING REGION
CHIMERIC tRNA-ANTISENSE RNA GENE

FIG. 6

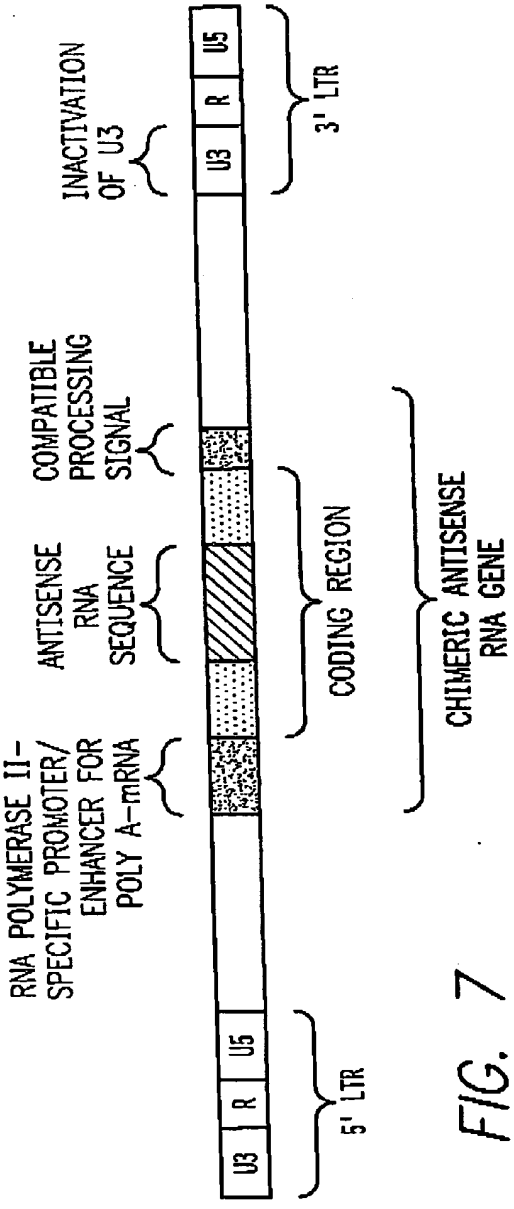
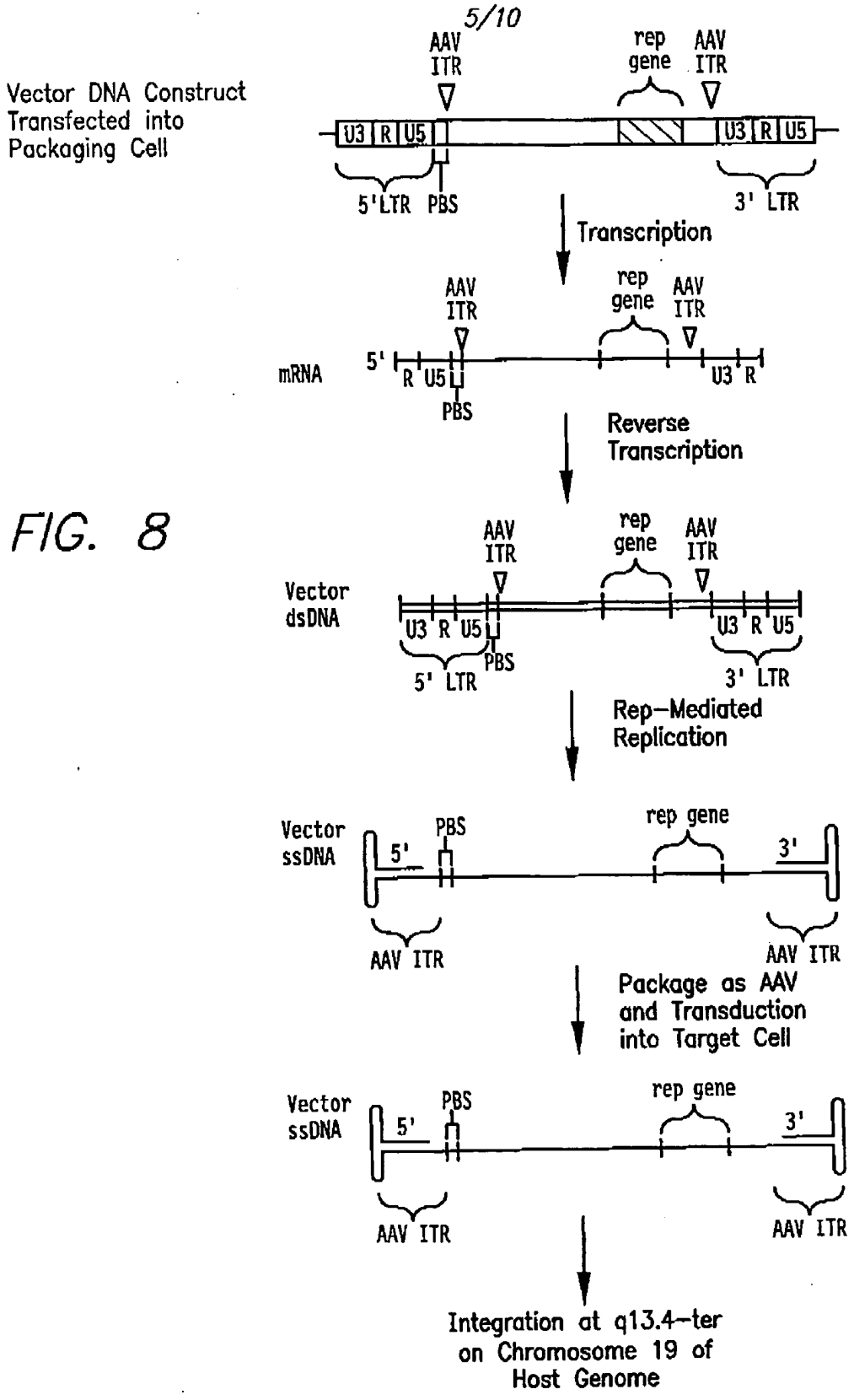

RNA POLYMERASE II-SPECIFIC PROMOTER/ ENHANCER FOR POLY A-mRNA
ANTISENSE RNA SEQUENCE
COMPATIBLE PROCESSING SIGNAL
INACTIVATION OF U3
U3
R
U5
5' LTR
3' LTR
CODING REGION
CHIMERIC ANTISENSE RNA GENE

FIG. 7

FIG. 8


Vector DNA Construct Transfected into Packaging Cell
AAV ITR
rep gene
AAV ITR
U3 R U5
U3 R U5
5'LTR PBS
3' LTR
Transcription
mRNA
5'
R U5
PBS
U3 R
Reverse Transcription
Vector dsDNA
5' LTR
3' LTR
Rep-Mediated Replication
Vector ssDNA
PBS
5'
3'
AAV ITR
Package as AAV and Transduction into Target Cell
Integration at q13.4-ter on Chromosome 19 of Host Genome

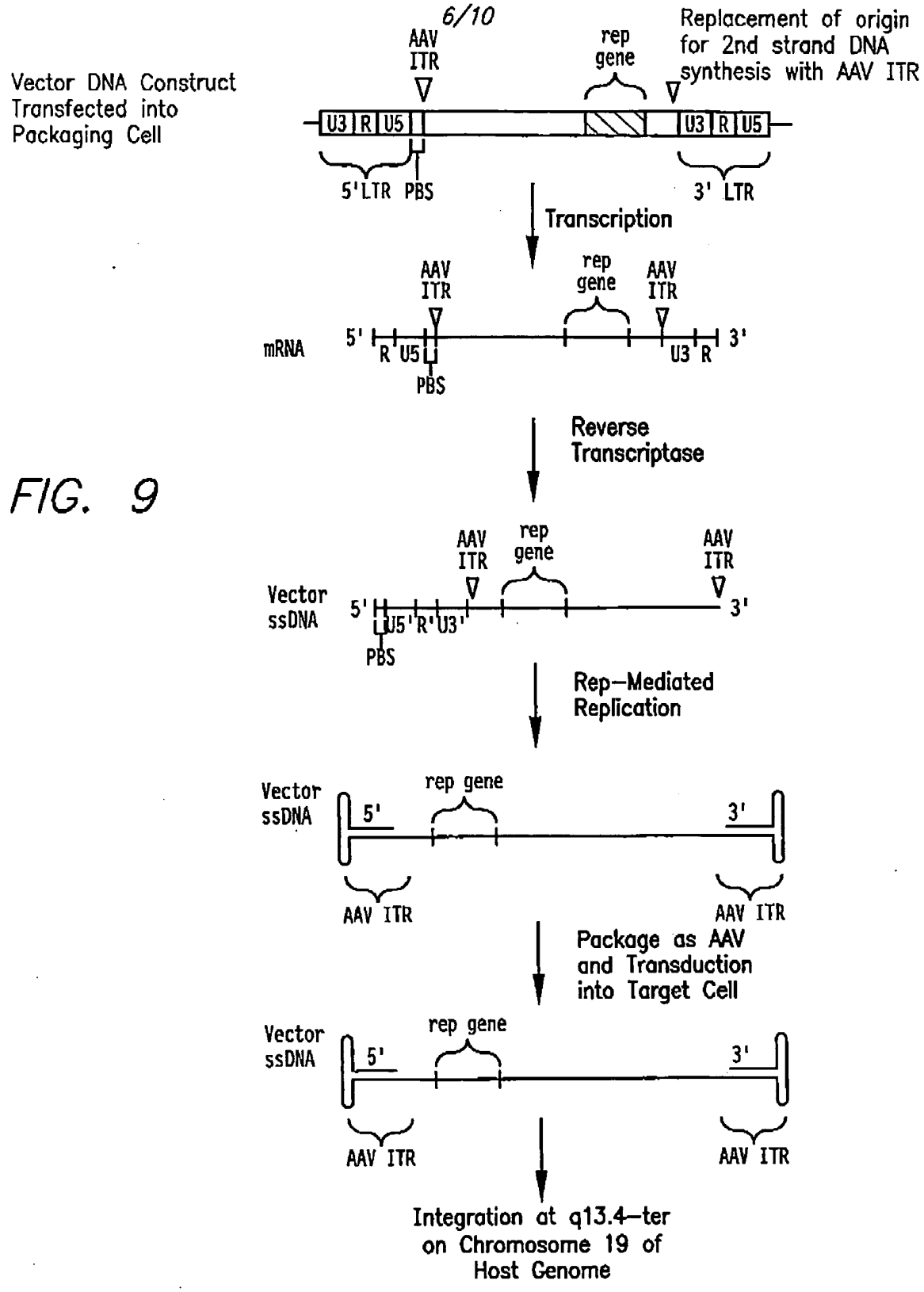

Vector DNA Construct Transfected into Packaging Cell
AAV ITR
rep gene
Replacement of origin for 2nd strand DNA synthesis with AAV ITR
U3 R U5
U3 R U5
5'LTR PBS
3' LTR
Transcription
AAV ITR
rep gene
AAV ITR
mRNA
5'
R U5
PBS
U3 R
3'
Reverse Transcriptase
AAV ITR
rep gene
AAV ITR
Vector ssDNA
5'
U5 R U3
3'
PBS
Rep-Mediated Replication
Vector ssDNA
rep gene
5'
3'
AAV ITR
AAV ITR
Package as AAV and Transduction into Target Cell
Vector ssDNA
rep gene
5'
3'
AAV ITR
AAV ITR
Integration at q13.4-ter on Chromosome 19 of Host Genome

FIG. 9

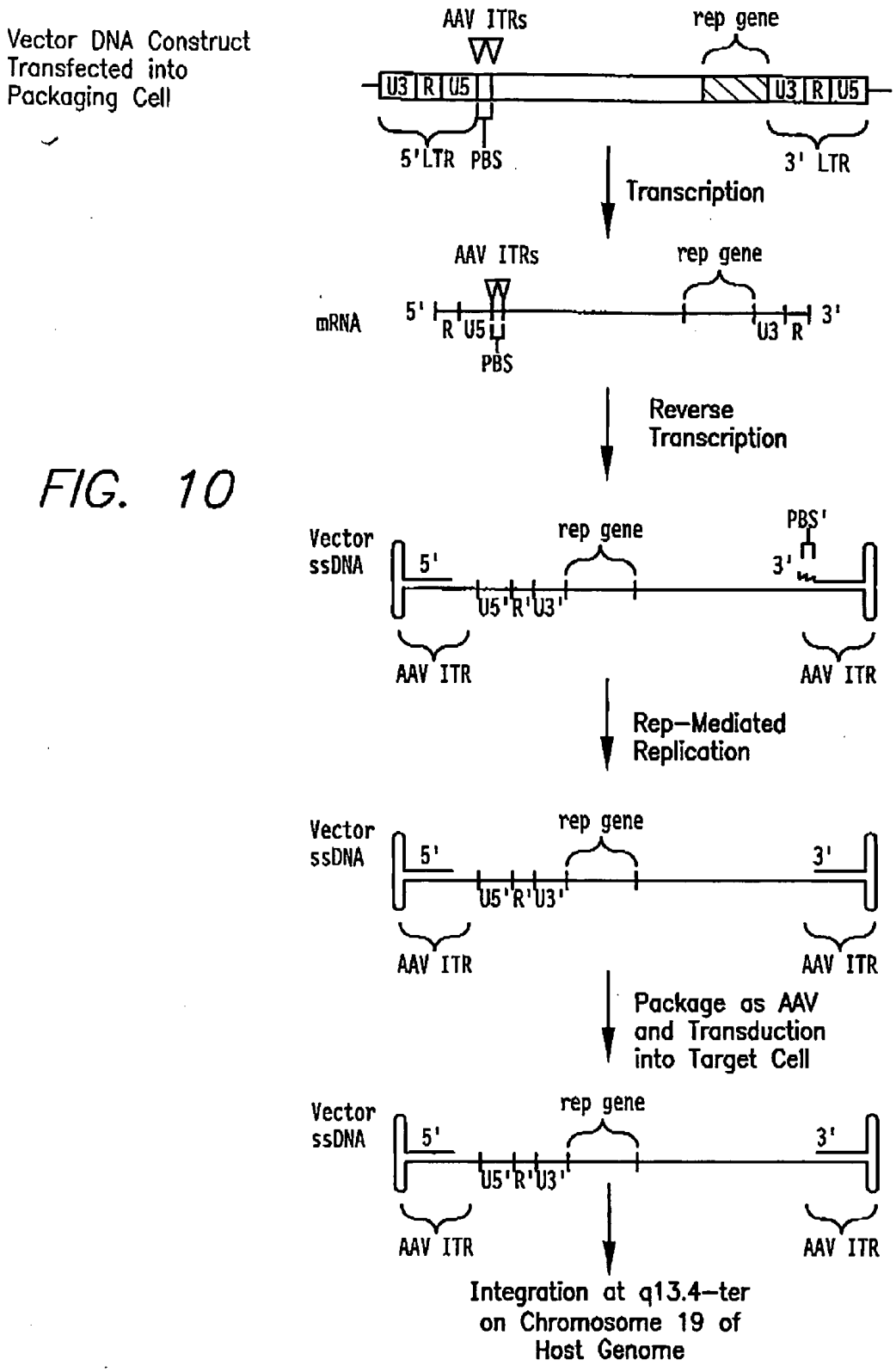

Vector DNA Construct Transfected into Packaging Cell
AAV ITRs
rep gene
U3 R U5
U3 R U5
5'LTR PBS
3' LTR
Transcription
AAV ITRs
rep gene
mRNA
5'
R U5
PBS
U3 R
3'
Reverse Transcription
Vector ssDNA
rep gene
PBS'
5'
3'
U5'R'U3'
AAV ITR
AAV ITR
Rep-Mediated Replication
Vector ssDNA
rep gene
5'
3'
U5'R'U3'
AAV ITR
AAV ITR
Package as AAV and Transduction into Target Cell
Vector ssDNA
rep gene
5'
3'
U5'R'U3'
AAV ITR
AAV ITR
Integration at q13.4-ter on Chromosome 19 of Host Genome

FIG. 10

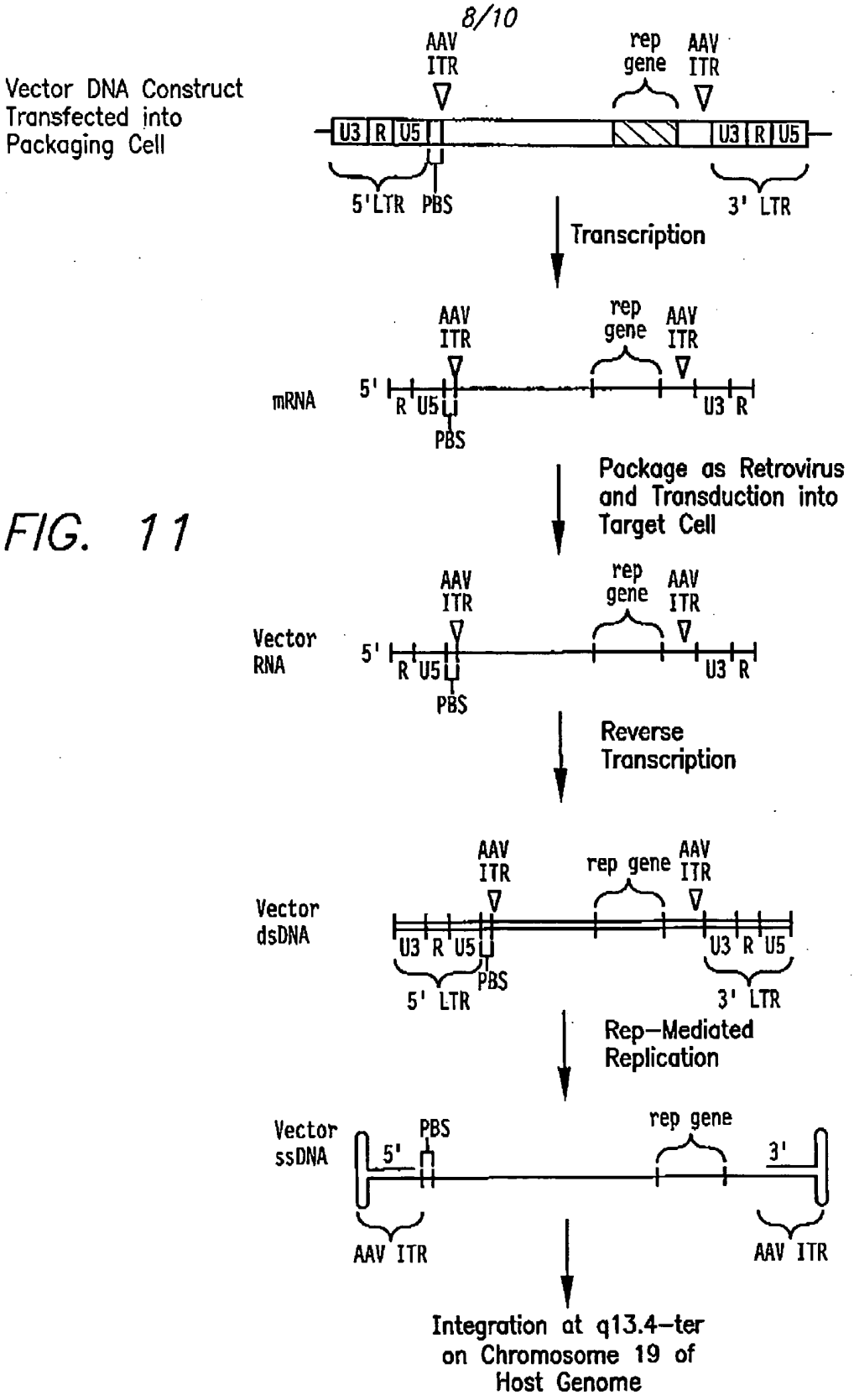
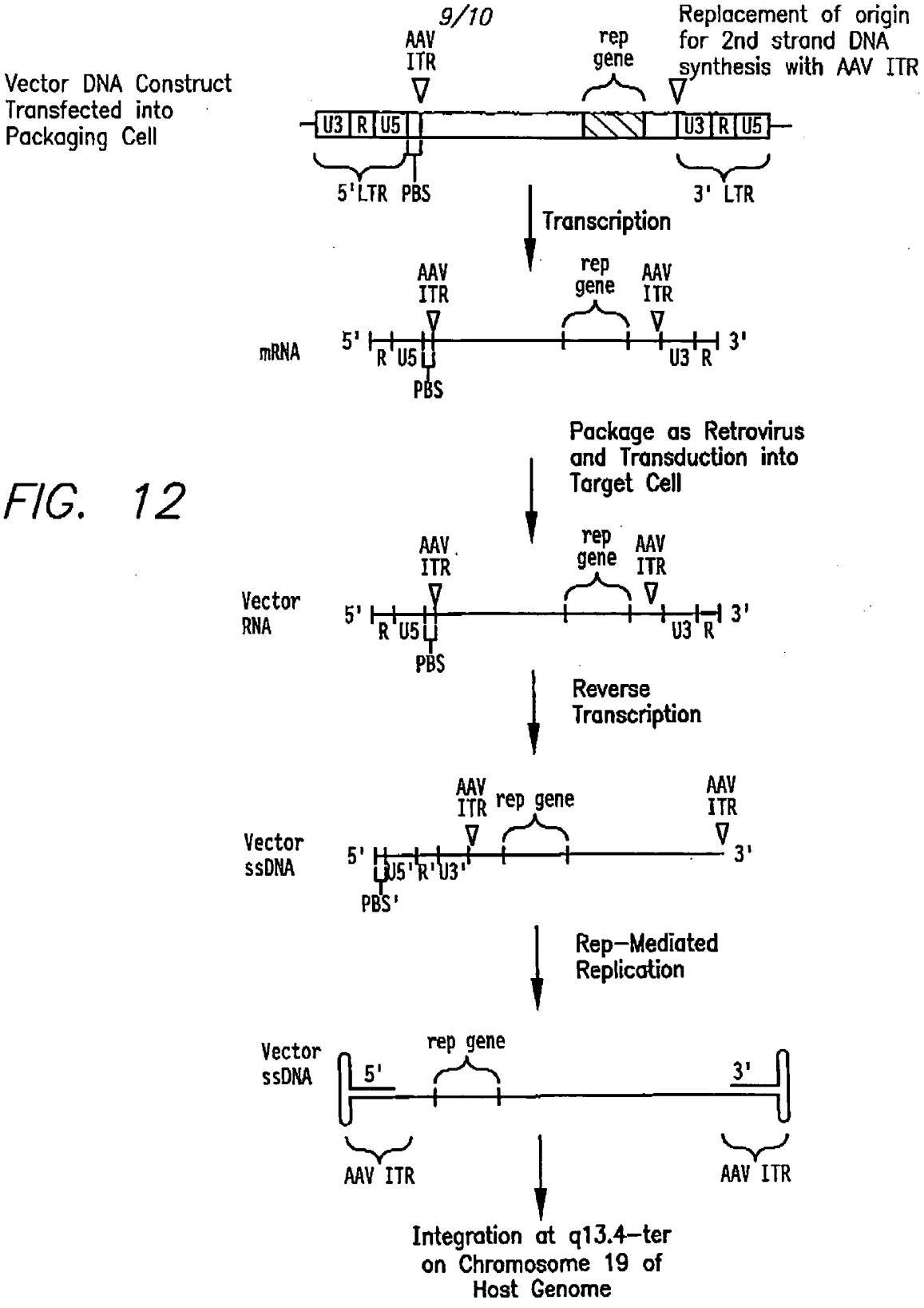

Vector DNA Construct Transfected into Packaging Cell
AAV ITR
rep gene
AAV ITR
U3 R U5
U3 R U5
5'LTR PBS
3' LTR
Transcription
mRNA
5'
R U5
PBS
U3 R
Package as Retrovirus and Transduction into Target Cell
Vector RNA
Reverse Transcription
Vector dsDNA
rep gene
5' LTR
3' LTR
Rep-Mediated Replication
Vector ssDNA
PBS
5'
3'
AAV ITR
Integration at q13.4-ter on Chromosome 19 of Host Genome

FIG. 11

FIG. 12


Vector DNA Construct Transfected into Packaging Cell
AAV ITR
rep gene
Replacement of origin for 2nd strand DNA synthesis with AAV ITR
U3 R U5
U3 R U5
5' LTR PBS
3' LTR
Transcription
mRNA
5'
R U5
PBS
U3 R
3'
Package as Retrovirus and Transduction into Target Cell
Vector RNA
Reverse Transcription
Vector ssDNA
rep gene
U5' R' U3'
PBS'
Rep-Mediated Replication
Integration at q13.4-ter on Chromosome 19 of Host Genome

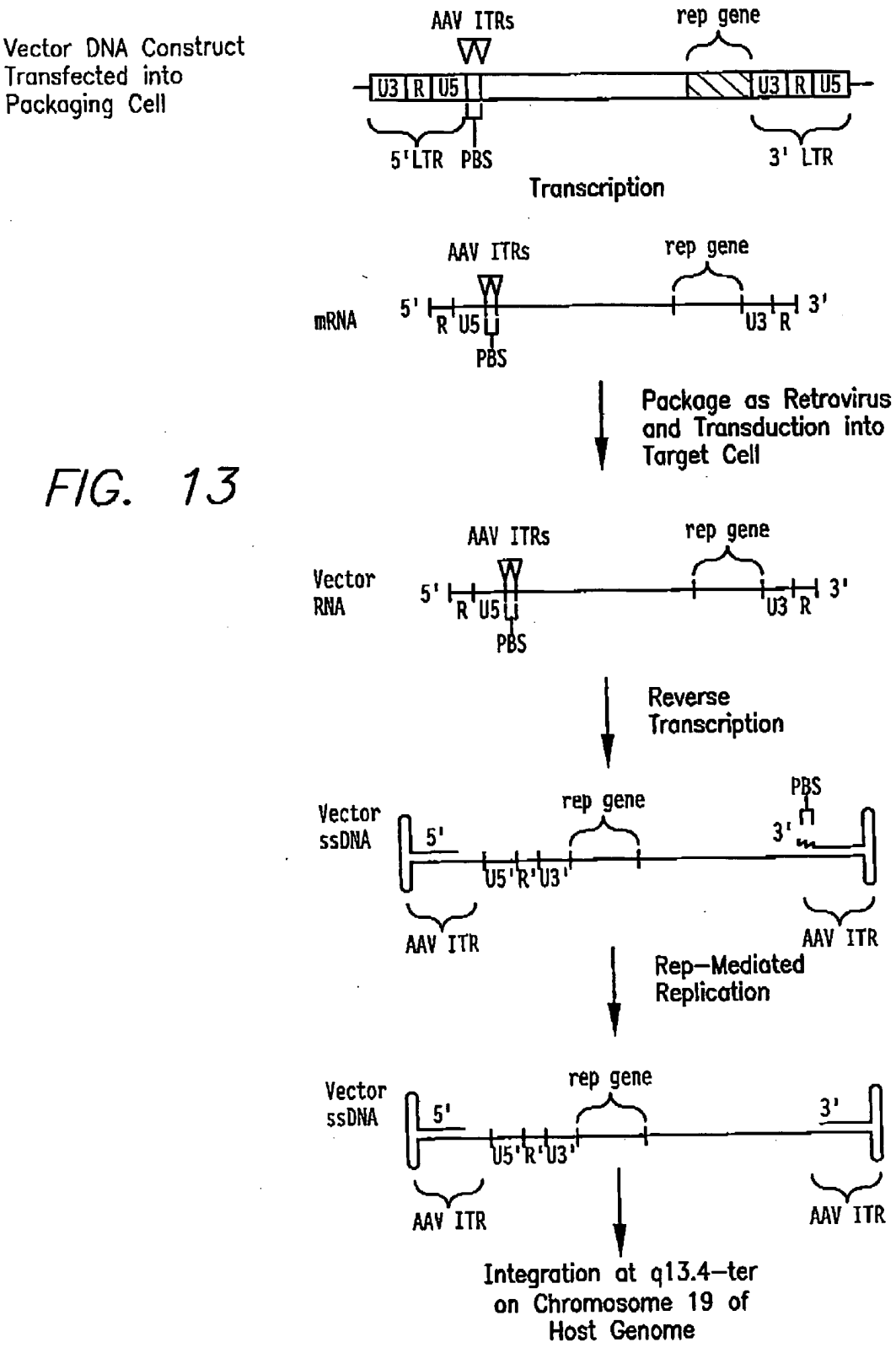

Vector DNA Construct Transfected into Packaging Cell
AAV ITRs
rep gene
U3 R U5
U3 R U5
5'LTR PBS
3' LTR
Transcription
AAV ITRs
rep gene
mRNA
5'
R U5
PBS
U3 R
3'
Package as Retrovirus and Transduction into Target Cell
AAV ITRs
rep gene
Vector RNA
5'
R U5
PBS
U3 R
3'
Reverse Transcription
Vector ssDNA
rep gene
PBS
5'
3'
U5 R U3
AAV ITR
AAV ITR
Rep-Mediated Replication
Vector ssDNA
rep gene
5'
3'
U5 R U3
AAV ITR
AAV ITR
Integration at q13.4-ter on Chromosome 19 of Host Genome

FIG. 13